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Case-Based Review: meningioma

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Meningioma is by far the most common primary intracranial tumor in adults. Treatment of meningioma is complex due to a tremendous amount of variability in tumor behavior. Many patients are incidentally found to have tumors that will remain asymptomatic throughout their lives. It is important to identify these patients so that they can be spared from potentially morbid interventions. On the other end of the spectrum, high-grade meningiomas can behave very aggressively. When treatment is necessary, surgical resection is the cornerstone of meningioma therapy. Studies spanning decades have demonstrated that extent of resection correlates with prognosis. Radiation therapy, either in the form of external beam radiation therapy or stereotactic radiosurgery, represents another important therapeutic tool that can be used in place of or as a supplement to surgery. There are no chemotherapeutic agents of proven efficacy against meningioma, and chemotherapy treatment is generally reserved for patients who have exhausted surgical and radiotherapy options. Ongoing and future studies will help to answer unresolved questions such as the optimum use of radiation in resected WHO grade II meningiomas and the efficacy of additional chemotherapy agents.

Keywords: chemotherapy, meningioma, radiation, radiosurgery, surgery.

Clinical Case Presentation

A 58-year-old man presented to his primary care physician with new right-sided subjective sensory abnormalities. He had no history of cancer. His general physical and neurological exams were normal. CT and MRI images of the brain were obtained (Fig. 1).

Epidemiology

Meningioma is the most common primary brain tumor diagnosed in the US, accounting for one-third of all primary central nervous system tumors.[1] Although the prevalence of pathologically confirmed meningioma is approximately 97.5 per 100 000 in the US, this is a significant underestimate of the actual prevalence.[1] Imaging demonstrates asymptomatic meningiomas in 0.9% of the adult population,[2] and autopsy studies suggest that the prevalence of meningioma is up to 3% in persons over 60 years of age.[3] World Health Organization (WHO) grade I meningiomas are more common in women, whereas higher-grade meningiomas have a slight male predominance.[1] Meningioma risk increases with age in both sexes.[1]

Ionizing radiation is a known risk factor for meningioma.[4,5] The risk is clearly increased among patients who have previously undergone therapeutic cranial radiation, such as long-term survivors of childhood brain tumors. Lower doses of radiation from medical diagnostic imaging or dental x-rays may also increase risk of meningioma, though this association is less well-established.[5] Nonionizing radiation from cellular telephone use has been proposed as a meningioma risk factor, but no convincing association has yet been demonstrated by epidemiological studies.[6]

A possible role for sex hormones in moderating meningioma risk is suggested by the higher rate of these tumors in women. Some studies have supported the idea that the use of exogenous sex hormone preparations, such as oral contraceptives or postmenopausal hormone replacement therapy, increases meningioma risk,[1,7,8] while other studies cast doubt on this association.[9] Overall, the data suggesting a positive association between exogenous hormone use and meningioma risk are stronger for

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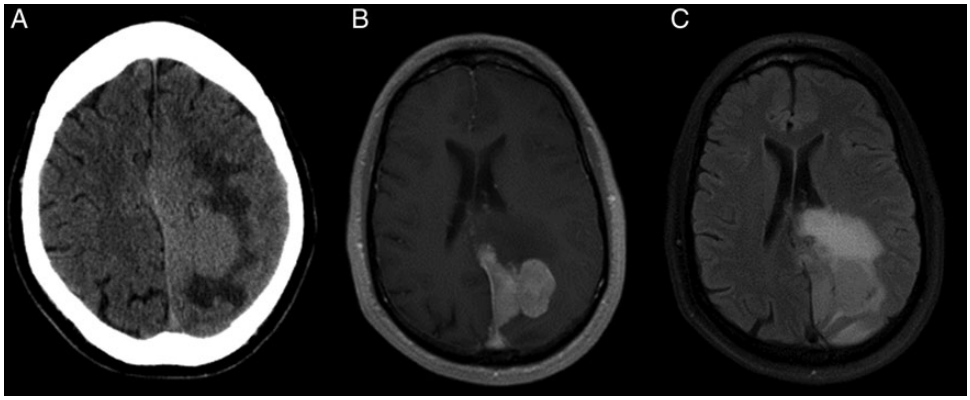

Fig. 1. (A) Unenhanced CT, (B) Postgadolinium spin echo T1-weighted, and (C) T2-weighted FLAIR images depict a relatively circumscribed mass impressed into the left superior temporal lobe with both solid, enhancing components and some cystic or necrotic areas. Moderate edema signal surrounds a portion of the mass.

postmenopausal hormone replacement than for oral contraceptive use. Though some studies have suggested an association between breast cancer and meningioma,[10] this is likely due to shared risk factors rather than a causal association.[11]

Neurofibromatosis type 2 (NF2) is a familial tumor predisposition syndrome with neurological manifestations including greatly increased risk of schwannomas and meningiomas, which are often multiple. The causative mutation, in the *NF2* tumor suppressor gene, was the first single-gene mutation directly associated with meningioma risk.[12,13] The *NF2* gene, which encodes the protein merlin, is inactivated in neurofibromatosis-associated meningiomas and in 30% to 70% of sporadic meningiomas.[14,15] Commonly, a two-hit mechanism of inactivation is observed, where a splice site, nonsense or frame-shift mutation disrupts *NF2* in one allele, and the second allele is disrupted by loss of some or all of chromosome 22.[16] Merlin is involved in the regulation of contact-dependent inhibition of cellular proliferation through the coordination of multiple signaling pathways, but the exact mechanism by which it acts as a tumor suppressor is still unclear.[17] Studies have also shown that inactivation of merlin in meningioma cell lines leads to activation of the mTOR pathway.[18,19]

Meningiomas have also been reported with other genetic syndromes[20] including neurofibromatosis type 1 (*NF1*),[21] nevoid basal cell carcinoma (Gorlin syndrome [*PTCH*]),[22] Li-Fraumeni syndrome (*TP53* and *CHEK2*),[23] von Hippel-Lindau syndrome (*VHL*),[24] and Cowden disease (*PTEN*).[25]

Clinical Case Relevance

Like most patients with meningiomas, the patient in this case had neither a history of radiation exposure nor any known tumor predisposition syndrome. He had one second-degree relative who was being followed radiographically for a presumed meningioma, and he was advised that this was more likely to be a coincidence than a sign of a familial risk.

Initial Supportive Care

Meningiomas can arise anywhere in the dura surrounding the brain or spine, or rarely in locations without an apparent dural connection, but they most commonly present either along the skull base or over the cerebral hemispheres. Presenting symptoms vary with location, but headaches or seizures are common, as are subacutely progressive neurological deficits. Hemispheric tumors may present with hemiparesis or hemisensory loss, while skull base lesions may present with vision loss or dysfunction of other cranial nerves.

Antiepileptic Therapy

Patients who present with seizures should be treated with antiepileptic drug (AED) therapy. As with other brain tumors, the ideal medication would have rapid onset of efficacy with minimal risk of side effects or drug interactions. For patients with meningioma who have not had a seizure, there is no proven role for long-term prophylactic AED therapy, and the American Academy of Neurology recommends against the routine use of prophylactic AEDs outside of the immediate perioperative period.[26]

Corticosteroid Therapy

Meningiomas may increase intracranial pressure and cause symptoms such as headaches or focal neurological deficits either directly, due to their nature as space-occupying lesions, or indirectly, by causing peritumoral vasogenic cerebral edema. However, in contrast to patients with other brain tumors such as high-grade glioma, many patients with meningioma have little or no vasogenic edema even when the meningioma is quite large. Thus, treatment with corticosteroids should be reserved for symptomatic patients with imaging evidence of peritumoral edema. When indicated, dexamethasone can be started at doses as high as 16 mg daily in 4 divided doses, and subsequently tapered down to the lowest effective dose or discontinued altogether. The biological half-life of dexamethasone is in excess of 36 hours, and daily or twice-daily dosing is effective and more convenient for maintenance therapy in most patients. Gastrointestinal ulcer prophylaxis and pneumocystis prophylaxis should be considered for patients in whom long-term corticosteroid treatment is anticipated.

Exogenous Hormone Therapy in Women

Premenopausal women who use hormonal contraceptive methods can continue them with little if any risk of stimulating

meningioma growth. However, some women prefer to use alternative birth control methods to avoid even the theoretical risk of triggering increased meningioma growth. For postmenopausal women on hormone replacement therapy, discontinuation of hormone therapy should be considered if it can be tolerated symptomatically.

Clinical Case Relevance

As the patient's symptoms were mild, and surgical resection was anticipated in the near future, no corticosteroid therapy was recommended. Likewise, in the absence of a seizure history, no antiepileptic therapy was prescribed.

Initial Diagnostic Imaging

Meningiomas are usually solitary, intracranial, dural-based masses that may be round (globose) or sheet-like (en plaque). Most meningiomas are well-demarcated, extra-axial masses with a broad dural attachment. They vary widely in size, but if large enough, will inwardly displace the underlying brain cortex. MRI studies often reveal a CSF-vascular cleft between the mass and the brain. Such clefts can be absent, however, particularly when high-grade meningioma invade the brain. En plaque meningiomas have a more infiltrative pattern along the dura. On the order of 4% of intracranial meningiomas have associated intratumoral or extratumoral cysts.[27]

On CT, most meningiomas are hyperdense or isodense relative to cortex. Frank necrosis or hemorrhage is uncommon. Fifteen to 20% of meningiomas demonstrate calcification on CT.[28] Bone changes associated with meningiomas are common and include hyperostosis and osteolysis. Such changes are not predictive of tumor grade, however. Hyperostosis, occurring in 20% of cases, varies from subtle to striking and is not proportional to tumor size.[29] Hyperostosis is frequently associated with tumor invasion of bone but may also be only a reactive phenomenon; it is often difficult to distinguish between these possibilities, but strong, homogeneous enhancement within hyperostotic bone makes tumor infiltration more likely. Figure 2 displays the CT appearance of hyperostosis in two patients with meningioma invading bone.

On MRI, meningiomas are typically isointense to mildly hypointense relative to cortex on T1-weighted images and are isointense to moderately hyperintense on T2-weighted images. Most meningiomas enhance strongly and homogeneously from gadolinium leakage out of their vasculature, and virtually all enhance at least to some degree, even those that are heavily calcified. A dural tail is seen postcontrast in most meningiomas and usually represents adjacent reactive dural thickening rather than tumoral extension.[30] The dural tail is not specific for meningioma; other dural neoplasms can demonstrate this finding. Meningiomas that are hypointense on T2-weighted images tend to have a harder consistency at surgery. It has been suggested that meningioma consistency at surgery (ie, hard vs soft), can be predicted more accurately using diffusion tensor imaging (DTI) measures such as fractional anisotropy and mean diffusivity.[31,32] Magnetic resonance elastography is an advanced MRI technique that may also be used to evaluate meningioma consistency.[33]

Peritumoral brain edema signal is seen in approximately 60% of meningiomas, and occurs with little correlation to tumor size.[34,35] There are multiple theories for why this edema develops, including hydrodynamic, venous obstruction and VEGF-related theories.[36] Although atypical and malignant meningiomas may cause edema by invading the brain, WHO grade I meningiomas frequently cause peritumoral brain edema without brain invasion. Therefore, the presence of peritumoral brain edema cannot be reliably used to distinguish between meningioma grades. The rare microcystic subtype of meningioma tends to have low signal intensity on T1-weighted images, high signal intensity on T2-weighted images, and relatively severe peritumoral brain edema.[37]

As meningiomas are vascular tumors, flow voids or enhancing vessels may be seen around and within them on MRI, sometimes with a "sunburst" appearance. Catheter angiography reveals the hypervascular nature of meningiomas, typically with robust arterial opacification and a strong and prolonged vascular "blush" that extends late into the venous phase (classically compared to an unwanted guest who arrives early and stays late). Dural branches of the external carotid artery, internal carotid artery,

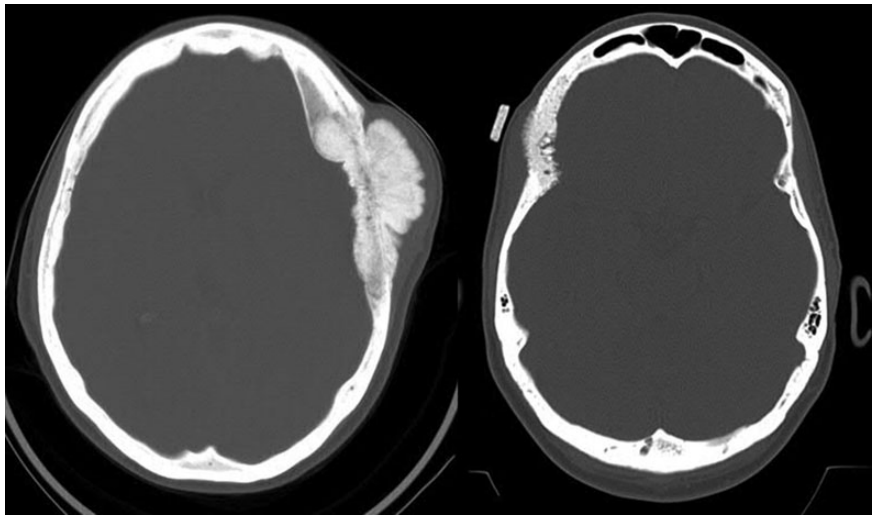

Fig. 2. CT appearance of cranial hyperostosis in 2 different patients with bone invasion of meningioma.

and vertebral artery may supply the tumor, and pial arteries may also become parasitized by the tumor. Meningiomas may encase arteries such as the internal carotid artery, sometimes narrowing them, though related hemodynamic impairment is rare. Meningiomas may invade into and obstruct venous structures such as the dural venous sinuses, which are best evaluated with gadolinium bolus MR venography (MRV) or catheter angiography.

Currently, it is difficult or impossible to distinguish between grade I meningiomas and grade II (atypical) and grade III (malignant) meningiomas with preoperative imaging. Loss of a distinct interface between tumor and brain raises the possibility of brain invasion and a higher-grade tumor, particularly if the tumor's interface with the brain is also irregular. Malignant meningiomas typically do invade brain, often with a "mushroom" configuration into the brain as well as with osteolysis of the overlying calvarium and extension into the scalp. Most meningiomas do not have substantially restricted diffusion on diffusion-weighted imaging. However, some have suggested that apparent diffusion coefficient and fractional anisotropy and other DTI parameters can be used to predict grade II/III meningiomas, though others have questioned this.[38–43] MR spectroscopy of meningiomas typically reveals elevated choline and decreased creatine. Elevated alanine, lactate, glutamine/glutamate, and lipid may also be present. Elevated lactate suggests aggressive meningioma behavior, even in tumors that are WHO grade I by histology.[44,45]

The differential diagnosis of meningioma includes dural metastases from primary tumors such as breast, lung, or prostate cancer, and these may be indistinguishable from meningioma. Granulomatous disease such as sarcoidosis and tuberculosis can also cause dural-based enhancing masses that mimic meningioma, though solitary dural granulomatous masses are not common. Focal idiopathic hypertrophic pachymeningitis is uncommon but can form enhancing masses in or around the skull base. Immunoglobulin G (IgG)4-related disease is a condition characterized by inflammatory pseudotumors that can involve the meninges. Generally, IgG4-related disease causes a diffuse thickening of the dura, but it can cause focal lesions that mimic meningioma.[46] A hemangioma of the dura may resemble a meningioma, though most hemangiomas are very hyperintense on T2-weighted imaging, which is not typical for meningioma. The solitary fibrous tumor of dura is uncommon and may be indistinguishable from meningioma. Hemangiopericytoma, now considered to be within the solitary fibrous tumor spectrum, is a WHO grade II or III meningeal-based tumor that does not calcify or cause hyperostosis and often has heterogeneous enhancement. These tumors may have a narrow and stalk-like or a broad-based dural attachment, often along the falx cerebri or tentorium cerebelli. Dural lymphoma and leukemia (granulocytic sarcoma) may also present as asymmetric enhancing dural masses or thickening. Extramedullary hematopoiesis may mimic en plaque meningioma or meningiomatosis. Sarcomas, including osteogenic sarcoma and Ewing sarcoma, are in the differential diagnosis for a biologically aggressive or malignant meningioma.

Clinical Case Relevance

Imaging demonstrated a large mass arising from the posterior falx with surrounding edema (Fig. 1). The patient had no history of cancer and no symptoms to suggest occult metastatic disease, so meningioma was strongly favored as the diagnosis. While edema can be seen in WHO grade I meningioma, its presence did increase the level of suspicion for a WHO grade II or III tumor. The tumor extended to the posterior third of the sagittal sinus, which was confirmed to be patent by MRV. Given that the patient was symptomatic and that there was concern for higher-grade meningioma, surgery was recommended.

Surgery

Goals of Surgery

The mainstay of meningioma treatment is surgical resection. The goal is complete resection of the lesion, the dura that gives rise to it, and any involved overlying bone. Donald Simpson demonstrated that meningioma recurrence risk is strongly related to the degree of surgical resection in his seminal 1957 work.[47] The 5 grades of resection that he described have since been used extensively in clinical practice and research to evaluate the degree of resection and inform the need for adjuvant treatment (Table 1). However, over the past 6 decades, evolving data and clinical practice have led to a reconsideration of the surgical goals of meningioma treatment. Many would now argue that degree of surgical resection is most directly related to recurrence of grade I meningiomas, though population-based data suggest a correlation between extent of resection and survival in high-grade meningioma as well.[48] Today, surgeons are able to offer safe and effective treatments for tumors in locations such as the skull base that were historically considered inaccessible. Additionally, improved imaging has allowed for the identification of miniscule areas of residual or recurrent tumor.

Lesions growing along the skull base are not well served by the rudimentary Simpson grading system with respect to their recurrence potential. First, although the concept of degree of resection is intuitively obvious for convexity lesions, it is less applicable along the skull base, where anything but a Simpson grade IV resection is often unrealistic. In this setting, a small amount of tumor left in close proximity to a cranial nerve likely confers a very different recurrence potential than the average Simpson grade IV resection of a convexity lesion included in Simpson's original paper. Several authors have suggested alternative classification systems that are more applicable to skull base tumors but none have become widely adopted.[49,50] A number of authors have also shown that in modern studies there may be little

Table 1. Simpson classification of extent of meningioma resection

Simpson grade	Definition
I	Macroscopically complete removal including excision of the dural attachment and of any abnormal bone.
II	Macroscopically complete removal with coagulation of the dural attachment but without removal of underlying bone.
III	Macroscopically complete removal of the intradural tumor, without resection of the dural attachment or underlying bone.
IV	Subtotal resection.
V	Simple decompression, with or without biopsy.

difference in recurrence among Simpson grades I, II, and III.[51,52] Although most data would support the low rates of recurrence observed with Simpson grade I resections, lesser degrees of resection may be in fact equally efficacious and safer.

Attempted gross total resection remains the current surgical best practice for any meningioma. However, today more than ever, small residuals, particularly along the skull base or in close proximity to neurovascular structures, can safely be left in situ for either observation or adjuvant treatment with radiosurgery. The long-term efficacy of such hybrid approaches is not entirely known; however, most early data would suggest this is a safe and effective treatment strategy.[53,54]

Atypical and malignant meningiomas pose special challenges to the neurosurgeon. A Simpson grade I resection should be the goal for these tumors, yet it does not confer the same excellent prognosis as in grade I meningiomas. The role of adjuvant radiation therapy to prevent recurrence following surgery will be discussed in the next section.

Recent widespread use of intracranial imaging has led to far more incidentally discovered asymptomatic meningiomas. Factors that must be considered when choosing an optimum patient-specific treatment strategy include tumor size and location, as well as the age and general health condition of the patient. As meningioma surgery can occasionally result in significant morbidity, judicious use of surgery is imperative.[55] While specific age cut-off points are not well established, the general view is that young patients with large tumors should be treated and older patients with small tumors are optimally observed with serial scans.[56] Radiographic evidence of progression should prompt treatment evaluation (surgical or radiosurgical) for the majority of asymptomatic lesions. Of particular importance are asymptomatic lesions along the skull base that can in many instances be observed at first presentation.

Surgical resectability of a meningioma depends on the presence of arachnoidal planes along the tumor that can be dissected in order to avoid cortical brain injury. Although there is some variability in the presence of such surgical planes among meningiomas at first presentation, recurrent tumor is almost guaranteed to lack such dissection planes. The surgical dictum that "The first time is the best time" applies to meningiomas, particularly along the skull base. Every effort should be made at first surgery to resect as much tumor as can safely be resected. Should some tumor be left behind to avoid injury to neurovascular structures, shaping and sizing of the residual to the size that could be treated with radiosurgery, although difficult at times, allows for optimal outcomes.

Surgical Technique

The majority of convexity lesions are best approached via a convexity craniotomy that allows for exposure of the entire tumor and a margin of dura around the lesion in order to optimize the extent of resection. Lesions along the major dural venous sinuses require special attention. Aggressive treatment of such lesions with resection of the dural sinus can lead to less than optimal patient outcomes.[57,58] Postoperative venous hypertension resulting from inadvertent venous occlusion or venous sacrifice can be devastating and lead to significant morbidity and even mortality. For most such lesions, the approach of choice is removal of all the tumor outside the venous sinus, coagulation of the sinus wall dura, and adjuvant radiosurgical treatment.[59]

Skull base meningiomas can occur along the anterior, middle, and posterior fossa. Although the sphenoid wing is the most common location, midline lesions (olfactory grove, tuberculum and planum meningiomas) are also quite common and often present with significant visual impairment. Skull base approach adjuncts such as orbital and zygomatic osteotomies have traditionally been employed to allow for a shorter and wider surgical corridor to the lesion.

Over the past decade endoscopic transnasal approaches have been increasingly popularized for midline anterior and middle skull base meningiomas.[60–62] The subcranial axis of approach into such lesions obviates the need for brain retraction and together with the early devascularization that such an approach affords, makes the expanded transsphenoidal or endonasal endoscopic approach a valuable addition to the surgical treatment of such lesions. Increased postoperative CSF leak and infection rates, as well as difficult-to-control bleeding points through such a long and narrow corridor, remain major impediments in the widespread adoption of endoscopic techniques. The rate of postoperative CSF leak can be reduced by the use of vascular endonasal flaps, which are typically performed by ENT surgeons in skull base reconstruction.[63]

Posterior fossa meningiomas are likely some of the most challenging lesions along the skull base, especially those that involve the petroclival junction and extend into the middle fossa or the cavernous sinus. Such lesions are located anterior to the cranial nerves, displace the brainstem, and encase blood vessels. Improvements in surgical technique have made these very difficult lesions treatable, albeit at times with significant neurologic morbidity.[64,65] Hybrid strategies of maximal safe surgical tumor resection combined with radiosurgery to the residual tumor are often the best options for treatment of lesions in this region.

The role of preoperative planning with high resolution MRI, particularly DTI and noninvasive vascular imaging, as well as tumor embolization, is crucial for many meningiomas.[66,67] Preoperative localization of functional regions within the brain can be invaluable in surgical planning, and may help avoid devastating postoperative neurological deficits. Many skull base meningiomas, including large and giant convexity meningiomas, can benefit from embolization of even part of their feeding arteries in an effort to minimize the blood loss and operative time during surgery.

Clinical Case Relevance

The patient underwent extensive subtotal resection of a WHO grade II meningioma. Figure 4 shows preoperative and postoperative MR images. A small amount of tumor that had invaded the posterior portion of the sagittal sinus was unresectable. The patient's sensory symptoms resolved after surgery.

Pathology

Meningioma Grading

The histological diagnosis in this case was atypical meningioma (WHO grade II). The tumor was characterized by a meningothelial cell proliferation showing increased mitotic activity, with up to 7 mitoses per 10 high-power fields (Fig. 3A). Focal areas showing chordoid features were also identified (Fig. 3B).

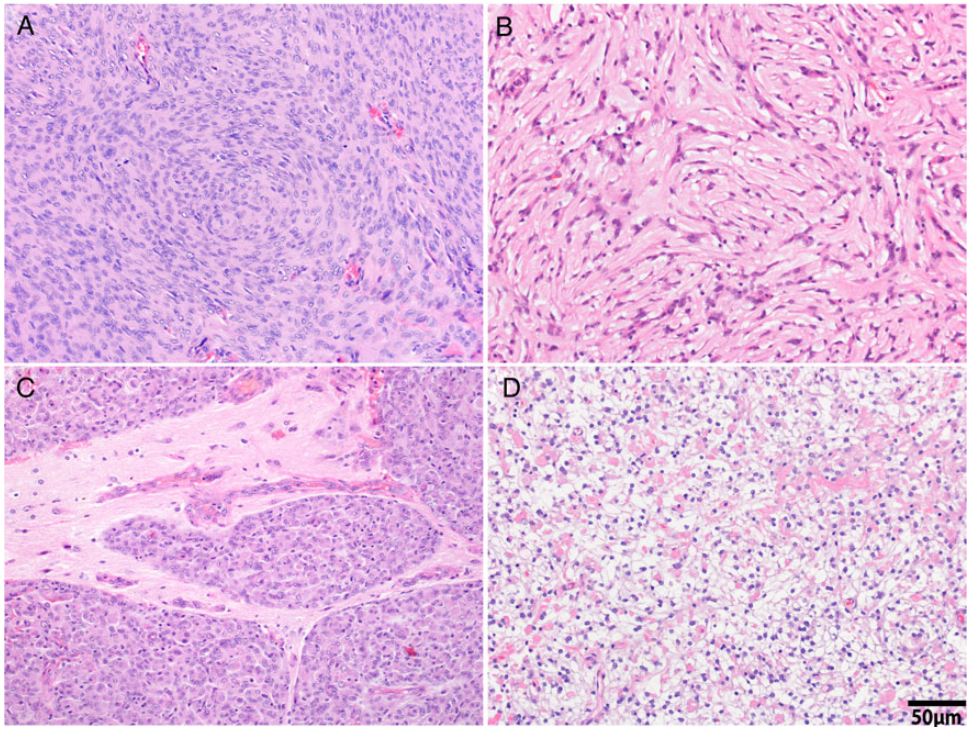

Fig. 3. The biopsies demonstrated a meningothelial cell proliferation with (A) elevated mitotic activity, showing up to 7 mitoses per 10 high-power fields. (B) Focal areas with chordoid features were identified, which formed a minor component of this meningioma. (C) Invasion of the brain parenchyma by irregular protrusions of meningioma would warrant a WHO grade II designation. Meningioma composed of over 50% of (B) chordoid or (D) clear cell variants also warrant a WHO grade II designation. (Hematoxylin and eosin stained sections at 200x magnification. Scale: 50 μm).

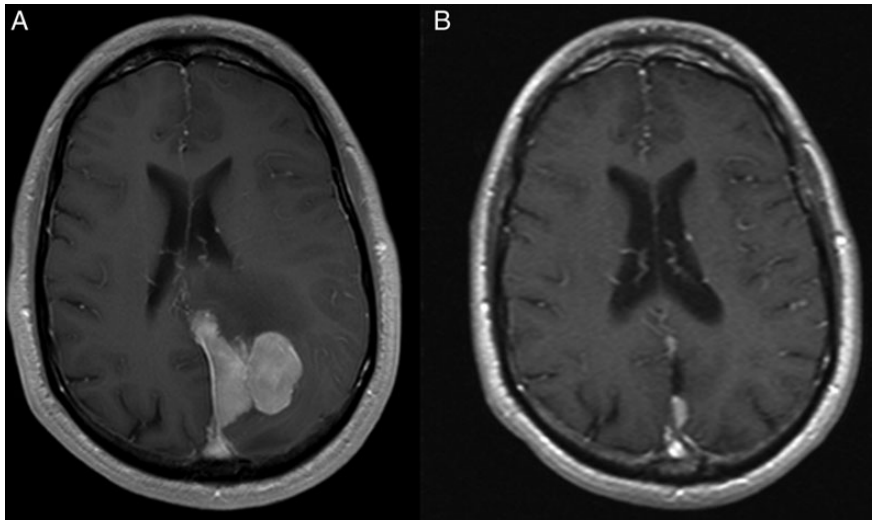

Fig. 4. (A) Preoperative and (B) postoperative, postgadolinium T1-weighted MR images demonstrate extensive subtotal resection of a falcine meningioma.

Meningiomas are meningothelial neoplasms that arise from arachnoid cap cells. Most meningiomas are WHO grade I tumors. A number of different morphologic subtypes of WHO grade I meningioma exist, including meningothelial, fibrous, transitional, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich, and metaplastic variants. The morphologic variants of WHO grade I meningioma are treated the same and all carry an excellent prognosis. Most WHO grade I meningiomas will remain WHO grade I, though recurrence as a more aggressive WHO grade II or III tumor can occur.

Diagnostic features of atypical (WHO grade II) meningioma include increased mitotic activity relative to WHO grade I tumors, with 4 or more mitoses identified per 10 high-power fields (400x magnification, corresponding to 0.16 mm^2), or the presence of 3 or more of the following histological features: hypercellularity, prominent macronucleoli (easily observed at 100x magnification), uninterrupted patternless growth ("sheeting"), small cells with a high nuclear to cytoplasmic ratio, and foci of spontaneous necrosis in the absence of prior embolization.[68,69] Cases with invasion of the brain parenchyma (Fig. 3C) have similar rates of recurrence and mortality, and so warrant a WHO grade II designation. Furthermore, chordoid and clear cell meningioma variants are also associated with more aggressive clinical behavior, and are also designated WHO grade II when these variants comprise more than 50% of the tumor. Clear cell meningioma is a rare meningioma variant composed of polygonal cells with clear, glycogen-rich cytoplasm and prominent interstitial and perivascular collagen (Fig. 3D), while chordoid meningioma is predominantly composed of thin trabeculae of eosinophilic and vacuolated meningothelial cells within a myxoid background (Fig. 3B). In our case, while focal areas showed histological features of chordoid meningioma, these comprised only a small proportion of the tumor. Thus, we designated this tumor a WHO grade II meningioma based on the elevated mitotic activity.

Anaplastic meningiomas are defined by the presence of frankly malignant cytological anaplasia or a markedly elevated mitotic rate of 20 or more mitoses per 10 high-power fields. These tumors exhibit very aggressive clinical behavior and are categorized as WHO grade III tumors. Similarly, papillary and rhabdoid meningioma variants exhibit very aggressive clinical behavior and are also designated WHO grade III when they comprise more than 50% of the tumor. The significance of focal areas showing features of papillary or rhabdoid meningioma is uncertain.

At present, meningiomas continue to be graded based on histological features per WHO guidelines. However, some degree of subjectivity is inherent in purely histological grading. In the future, genomic information is very likely to inform risk stratification and aid in the development of molecularly guided therapies for patients with meningioma. Multi-institutional collaborative studies are necessary to identify such prognostically and therapeutically relevant markers in meningioma.

Molecular Pathology

Several recent studies have more comprehensively characterized the genomic landscape of meningiomas.[70,71] Meningiomas are generally genomically less complex than most other tumor types. However, the various meningioma subtypes and grades are enriched for particular copy number alterations and mutant genes. Approximately 40% of WHO grade I meningiomas do not demonstrate any recurrent copy number aberrations.[72] These copy-neutral meningiomas are often meningothelial or secretory meningioma subtypes. Angiomatous and microcystic meningioma are characterized by polysomies of many chromosomes.[73] The most common copy number change in WHO grade I meningioma is monosomy of chromosome 22, which results in single copy loss of the *NF2* gene on 22q12.[15,74] This frequent somatic loss of the *NF2* gene in sporadic tumors is predictable, given the previously discussed increased risk of meningioma associated with germline *NF2* mutation. Meningioma arising in the cranial convexities are more likely to harbor monosomy 22 and mutations in *NF2* than are meningioma arising in the skull base.[75,76] Higher-grade meningiomas typically have more copy number changes and more complex karyotypes[77] than lower-grade tumors. These changes include low-level copy number gains of 1q, 9q, 12q, 15q, 17q and 20q, and commonly encountered single-copy losses of 1p, 6q, 9p, 10, 14q, and 18q.[78–84] Proliferation, invasive growth, and recurrence among meningiomas are correlated with the number of chromosomal aberrations.[77,85] A recent study has shown that the number of copy number aberrations in atypical meningioma following gross total resection is strongly associated with recurrence risk.[86]

Recent studies have characterized the mutational profiles of meningioma using whole exome and genome sequencing approaches and have elucidated oncogenic drivers in meningioma that lack mutations in *NF2*.[71,75,87–89] For example, alterations in SMO, AKT1, KLF4, and TRAF7 are mutually exclusive with NF2 alterations. Our understanding of these tumor mutations is beginning to influence clinical trial design. A phase 2 clinical trial sponsored by the Alliance for Clinical Trials in Oncology and the National Cancer Institute Cancer Therapy Evaluation Program is evaluating SMO and AKT inhibitors in progressive meningiomas with *SMO* and *AKT1* mutations (A071401). This trial will also have an arm testing FAK inhibitors in patients with progressive *NF2*-mutant meningioma. FAK is a nonreceptor protein tyrosine kinase that integrates signals from integrins and growth factor receptors, and low merlin levels have been shown to predict sensitivity to FAK inhibition.[90] Other alterations of unclear significance have been described in meningiomas. Genetic mutations in epigenetic modifiers were reported in approximately 8% of meningiomas; these include the histone demethylases *KDM5C* and *KDM6A*, and the SWI/SNF member *SMARCB1*. *TP53* mutations[91] and loss of *CDKN2A/CDKN2B* have been found in higher grade meningiomas.[92] Losses of CDKN2A/CDKN2B are strongly associated with poor outcome.

Despite advances in the understanding of the oncogenic drivers of meningioma development, genes involved in malignant progression are less well-defined. Notably, telomerase activity is increased in WHO grade II and III meningioma[93–98] and has also been associated with early recurrence among low-grade meningiomas.[99] C228T and C250T mutations in the promoter of the telomerase reverse transcriptase gene (*TERT*) have been identified in a small subset of meningioma, in particular in higher-grade tumors that demonstrate evidence of histologic progression.[100–102] Meningioma progression may also be related to epigenetic modifications. Significantly higher DNA methylation levels of *HOXA7*, *HOXA9*, and *HOXA10* genes, and silencing of the *MAL2* gene by promoter hypermethylation are associated with higher meningioma grade and more frequent recurrence.[103–105] Further, anaplastic meningiomas show lower levels of global DNA methylation than WHO grade I meningiomas.[105] Consistent with this, mutations have been identified in a range of epigenetic modifiers, yet these are nonrecurrent and infrequently identified.[75,87,101]

Clinical Case Relevance

While molecular drivers of tumor behavior are becoming better understood, the principal pathological factor that currently informs clinical decision making regarding initial treatment of

meningioma is WHO grade. The diagnosis of WHO grade II meningioma in this case will have significant relevance for treatment planning.

Radiation Therapy

Radiation can serve many roles in the treatment of patients with meningioma. It can be used after initial surgery for patients perceived to be at a high risk of recurrence, as a primary therapy for patients who are ineligible for surgery, or as a treatment for recurrent disease. In each of these scenarios, the therapy may be delivered in a number of different ways. Unsurprisingly, the sheer number of ways that radiation therapy can be used to treat meningioma sometimes leads to uncertainty as to which approach is best for a given patient.[106,107]

As previously outlined, complete resection is considered definitive therapy for WHO grade I tumors. However, a variety of clinical factors can limit the surgeon's ability to achieve a complete resection. In the absence of adjuvant radiation, the long-term risk of tumor recurrence in this setting is high. Early studies evaluating the efficacy of radiation therapy in tumors that had been subtotally resected indicated substantial improvement in local control.[108–110] More modern experiences with improved radiation techniques have indicated local control rates equivalent to complete surgical resection.[110] Currently, most patients are observed after gross total or near total resection of grade I meningioma. Adjuvant radiation therapy is recommended if there is a large amount of unresectable residual tumor, or even a small amount of residual tumor in a location where tumor growth would be likely to produce morbidity.

In patients with higher-grade tumors, radiation may play a role even in the setting of a gross total resection. However, the role of radiation therapy following a gross total resection of WHO grade II tumors is controversial. While some studies have reported a negligible impact on outcomes, many of these series examined heterogeneous patient populations and surgical and radiation techniques, as well as small numbers of patients.[111] Other studies have reported inferior outcomes when adjuvant radiation was not used even in the setting of a total resection.[112,113] The European ROAM/EORTC 1308 study, in which patients with completely resected atypical meningioma will be randomized to observation or EBRT, will address the issue prospectively, but the trial will be enrolling patients for the next decade with significant time thereafter for the data to mature before the final report.[114]

WHO grade III tumors behave very aggressively and the overall consensus is to offer adjuvant radiation therapy to all patients, regardless of the extent of resection. Numerous studies have demonstrated improved disease-free and overall survival times when adjuvant radiation therapy is used in this setting.[115–117]

Recurrent meningiomas tend to behave aggressively, with significantly higher rates of additional recurrence following surgery in the absence of adjuvant radiation. The evidence supporting the role of postoperative radiation therapy following recurrence, even in the setting of a gross total resection, is compelling and several studies have reported significant improvement in local control when radiation is combined with surgery. In patients with recurrent tumors that are treated with adjuvant radiation, 10-year local recurrence improved to 89% from 30% with surgery alone; other studies have demonstrated similar results.[108,118,119]

Radiation Techniques

The goal of radiation is to deliver therapeutic doses to the tumor while minimizing radiation to the surrounding structures. For WHO grade I meningiomas, doses of 50.4 to 54 Gy in 1.8 to 2-Gy fractions with 0.5 to 2-cm margins are generally used. For WHO grade II and III meningiomas, higher doses of approximately 60 Gy are often employed.[120] Doses may need to be decreased when tumors directly invade or are adjacent to critical structures such as optic nerves or chiasm. Modern techniques such as radiosurgery or intensity-modulated radiotherapy (IMRT) allow shaping of the radiation around the tumor to achieve these effects. Using the bone windows of the CT scan may also allow evaluation of the presence of hyperostotic bone indicating tumor involvement that should be included in the treatment field.

Side effects of radiation for meningioma are similar to side effects of radiation for other primary brain tumors and can include worsening or recurrence of the original presenting focal tumor symptoms, nausea, vomiting, or headaches. Depending on the location of the tumor, focal alopecia may develop along with skin erythema. Systemic symptoms such as fatigue can occur during or following the radiation. Patients are also counseled on the risk of late complications such as permanent damage to the eye or optic nerves or other focal deficits. While rare in the initial treatment setting, radiation necrosis may occur and require supportive or surgical management. Other late side effects such as hypopituitarism or neurocognitive deficits may occur, with the risk of these issues strongly influenced by tumor location and radiation dose.[108,121]

Stereotactic radiosurgery (SRS) is a radiation technique that delivers high doses of radiation to small, well-defined targets. Radiosurgery is usually performed in a single session, but it can also be divided in up to 5 fractions. Typically, size and location determine the appropriateness of single-fraction therapy. Smaller tumor size and locations away from eloquent structures are preferable for single-fraction treatment. Radiosurgery is often used to treat patients with tumors located in challenging surgical locations, such as the cavernous sinus. Excellent rates of control, above 95%, have been reported with this technique and the doses typically prescribed are 12 to 15 Gy to the periphery.[122–124] Significant peritumoral edema following SRS is relatively rare, but it can cause marked morbidity, and may necessitate long-term corticosteroid therapy, initiation of bevacizumab, or even surgery for treatment.[125] Thus, it may be preferable to avoid radiosurgery in locations where edema could be expected to cause severe symptoms.[126] Predictors of worsening edema after SRS include large tumor volume, increasing SRS dose, and invasion or compression of venous structures, particularly the sagittal sinus.[127] Less common side effects reported after radiosurgery include internal carotid artery stenosis, cyst formation, cranial nerve deficits, and necrosis.[128]

Clinical Outcomes of Radiation Therapy

The goal of radiation therapy is to prevent meningioma growth. Slow-growing tumors such as meningioma often do not decrease in size significantly following radiation therapy. Nonetheless, symptomatic improvement after radiation therapy has been widely reported even in the absence of radiographic evidence of tumor shrinkage.[129–133]

Reirradiation of Recurrent Meningiomas

Doses given to treat meningiomas in the upfront setting approach the limits of tissue tolerance in the adjacent normal brain. While surrounding tissues likely experience partial recovery, subsequent radiation therapy places the patient at increased risk of cerebral radiation injury. Despite this risk, the lack of systemic agents with proven activity against meningioma and the limitations of surgery can make reirradiation the best available option in some instances.

There are limited reports that systematically evaluate the efficacy and risks of reirradiation. Wojcieszynski et al reported on the feasibility of offering additional radiation in appropriate clinical scenarios to patients with limited treatment options. They evaluated 19 patients who received either fractionated or single-dose reirradiation, and while they reported no serious radiation toxicity, prognosis in this patient population was poor, likely due to intrinsic tumor properties. Of note, patients with low-grade tumors who underwent repeat radiation had longer time to progression.[134,135]

Radiation-Induced Meningiomas

Meningiomas that arise in the setting of a prior history of intracranial radiation have unique pathologic findings that likely contribute to their high rate of recurrence following treatment and higher propensity for multiple lesions.[136,137] There are limited reports of radiation treatment for these tumors. Jensen et al looked at 16 radiation-induced meningiomas treated with radiosurgery and did not note any differences in local control or complications compared with historical controls, indicating radiation therapy is likely safe in this setting.[138]

Clinical Case Relevance

Radiation therapy is recommended after subtotal resection of WHO grade II meningioma. In this situation, either fractionated radiation therapy or radiosurgery could have been considered. While only one focus of macroscopic tumor remained after surgery, there was concern for microscopic disease elsewhere along the posterior falx, so fractionated radiation therapy was recommended.

Chemotherapy

At this time, there are no chemotherapy agents that have been unambiguously demonstrated to be effective against meningiomas. The National Comprehensive Cancer Network (NCCN) guidelines currently list three drugs as options for meningioma: interferon alpha (category 2B), a somatostatin analogue (category 2A, only for patients whose tumors are positive on an octreotide scan), or sunitinib (category 2B).[139]

Previously Tested Agents

Numerous cytotoxic drugs such as hydroxyurea, temozolomide, and irinotecan have been tested, as have hormonal agents, including mifepristone (an antiprogesterone), tamoxifen (an antiestrogen), and somatostatin analogues such as octreotide and pasireotide. Molecularly targeted therapies against targets such as platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), and vascular endothelial growth factor (VEGF), have been explored. Of the molecularly targeted therapies, the antiangiogenic drug bevacizumab is the most-often used.[140]

In reviewing the literature for chemotherapy for treatment of meningiomas, there is significant heterogeneity in the studies that have been done to date with regard to what tumor grades and prior treatments are included and what outcomes are reported, making comparison across studies challenging. Kaley et al summarize the literature nicely in their recent Response Assessment in Neuro-Oncology review, and recommend that 6-month progression-free survival (PFS) be used as the primary outcome for trials testing chemotherapy in recurrent meningiomas.[141] For the purposes of this article, the authors focused on prospective clinical trials for recurrent meningiomas for which data could be separated out for grade II/III tumors and for which PFS-6 was reported or could be reliably calculated; the results are summarized in Table 2. Antiangiogenic agents appear to have some promise, though toxicity from these agents is a concern.[142,143] In particular, bevacizumab has been tested as a single agent in a phase 2 clinical trial that has completed accrual (NCT01125046). In addition, a phase 2 trial testing the combination of bevacizumab and everolimus was initiated, but was terminated early due to slow accrual (NCT00972335). Results have not yet been published for either trial.

Agents Currently Being Tested in Clinical Trials

Chemotherapy for meningioma has been an under-studied area, but this is beginning to change. Recent increased interest and collaboration among institutions will hopefully lead to a corresponding increase in clinical trials investigating chemotherapy treatment options, with the ultimate goal of improving clinical outcomes. Table 3 shows active phase 2 and phase 3 clinical trials for meningioma as of July 15, 2015, as listed on clinicaltrials.gov. Only trials primarily focused on meningioma are included; phase 2 trials that allow for meningioma enrollment among numerous other tumor types are not shown.

Table 2. Progression-free survival at 6 months in selected trials of chemotherapy for recurrent atypical or anaplastic meningioma

Drug category	Drug regimen	PFS-6	No. patients
Cytotoxic drugs			
	Hydroxyurea[146]	25%[a]	4
	Hydroxyurea/imatinib[147]	31%	13
Hormonal agents			
	Octreotide[148]	44%	9
	Octreotide[149]	25%[a]	8
	Sandostatin LAR[150]	29%[a]	7
	Pasireotide LAR[151]	17%	18
Targeted agents			
	Imatinib[152]	0%	10
	Gefitinib or erlotinib[153]	29%	17
	PTK787[154]	55%[a]	22
	Sunitinib[145]	42%	36

Abbreviations: PFS-6, Progression-free survival at 6 months.
[a]estimated.

Table 3. Currently active clinical trials of chemotherapeutic agents for treatment of meningioma

Agent	Target population	Trial ID number
Trabectedin	Recurrent grade II/III meningioma	NCT02234050
Everolimus + octreotide	Recurrent aggressive meningioma	NCT02333565
Dexanabinol	Recurrent brain cancer, including meningioma	NCT01654497
Optune (device)	Recurrent grade II/III meningioma	NCT01892397
Everolimus	Meningioma or vestibular schwannoma for which surgery is planned	NCT01880749
AR-42	NF2 with meningioma or vestibular schwannoma for which surgery is planned	NCT02282917

Abbreviations: NF2, neurofibromatosis type 2.

Clinical Case Relevance

The patient has not yet experienced tumor progression. Should this occur, the re-resection and radiation therapy options would be the preferred treatments. If no surgical or radiation options are available, chemotherapy will be considered, ideally as part of a clinical trial given the lack of proof for available options.

Follow-up Imaging

There is significant variation in how frequently follow-up imaging for meningiomas is performed, both for asymptomatic, untreated tumors and for postoperative and/or postradiation tumors. In the case of incidentally discovered tumors for which observation is recommended, one reasonable approach would be to reimage in 3 to 6 months to help exclude a biologically aggressive meningioma or meningioma mimic. If the presumed meningioma remains stable and asymptomatic, continued follow-up imaging at 1 to 2-year intervals with then progressively greater intervals over time should be performed. Radiographic follow-up does not need to continue indefinitely; 5 or 10 years of observation of a stable tumor is sufficient in most cases.

For postoperative and/or postradiation-treated meningiomas, the first scan after treatment is often obtained at 3 months or longer to allow early treatment-related imaging changes to resolve. Atypical and malignant meningiomas, both more likely to recur following surgical resection or radiation therapy, require more frequent follow-up imaging. Incomplete resections may also be followed more closely, particularly if radiation therapy is being reserved for salvage treatment at time of progression.

Clinical Case Relevance

The patient underwent MRI 3 months after the completion of radiation therapy, and annually thereafter. Surveillance imaging will continue as long as the patient's overall health would allow for additional treatment if tumor recurrence were to occur. If this had been a grade I tumor, a shorter observation period would be recommended, with clinical follow-up alone if no tumor growth was seen in the initial 5 to 10 years.

Prognosis and Survivorship

Overall survival of patients with meningioma varies markedly depending on WHO grade. However, interpreting survival statistics for the various meningioma grades in the existing literature is challenging.[144–146] The WHO grading system for meningiomas has been adapted several times in recent decades, limiting the applicability of older data to patients diagnosed today. Even more importantly, prognosis is heavily influenced by multiple factors such as patient age, tumor location, tumor grade, tumor molecular biological characteristics, and postsurgery treatment, which cannot be easily disassociated. In order to establish survival statistics for contemporary treatment, the Radiation Therapy Oncology Group (RTOG) 0539 trial enrolled patients with all meningioma grades with a primary end point of PFS at 3 years. In this trial, which has now closed to accrual, all patients with newly diagnosed, WHO grade I tumors were initially observed, and patients with recurrent grade I tumors or all grade II and III tumors received adjuvant radiation.[147]

When considering the prognosis of an incidentally detected meningioma, the likelihood of growth and a need for future treatment are the most important issues. In a meta-analysis, including 675 untreated meningioma patients, follow-up results revealed favorable tumor behavior for tumors with a diameter less than 2.5 cm. In this patient group, no tumor growth was observed over a time period of almost 5 years.[148] Logically speaking, however, every large meningioma must have at one point been a small meningioma, so these data do not allow incidentally discovered small meningiomas to simply be dismissed as unimportant. Nonetheless, as previously discussed, most patients with asymptomatic tumors can reasonably be observed as an initial strategy. A disadvantage of the wait-and-see strategy is that occasionally a tumor will behave more aggressively than anticipated and cause symptoms or grow to a size too large for stereotactic radiotherapy between serial scans. Therefore, the question of whether a patient with an incidental and asymptomatic, small meningioma should be followed with serial imaging remains unresolved, and patient preferences must be considered.

Most patients with histologically proven WHO grade I tumors have an almost normal life expectancy when followed and treated adequately. In a recent study, PFS at 10 years for patients with WHO grade I tumors was reported to be 97.5% and mean overall survival more than 10 years.[145,149] The probability for recurrence also depends on the Simpson grade of resection, as previously discussed. In the recent literature, the recurrence rate for WHO grade I meningiomas after gross total resection (Simpson grade I-III) is 7% to 23% after 5 years, 20% to 39% after 10 years, and 24% to 60% after 15 years.[140] Among patients with recurrent tumors, 8-year PFS was 11% with surgery alone and 78% with surgery in combination with radiotherapy. Similar results were found in a study by Taylor et al; 5-year PFS was 30% with surgery alone and 88% in combination with radiotherapy.[118]

In WHO grade II meningiomas, which account for approximately 20% of all meningiomas according to the newest WHO criteria published in 2007, reported PFS varies significantly. Yang et al reported that only 35% of patients remain disease free at 10 years,[150] whereas another recent study reported that almost

70% of patients with WHO grade II tumors remain disease free at 10 years after combined treatment.[149] Other authors report that the PFS and survival rates among patients with WHO grade II meningiomas depend on Simpson grade resection. Following Simpson grade I-III resections, PFS varies between 48 and 96 month and following Simpson grade IV resections, it varies between 47 and 59 months.[146] Besides Simpson grade resection, Ki-67 index greater than 10%, age greater than 60 years, and parasellar/suprasellar tumor location were negative prognostic factors. Five-year overall survival for all patients in this study ranged between 80% and 100%.[146]

Estimates of PFS and overall survival in WHO grade III meningioma are highly variable. Five-year PFS after resection alone is reportedly 28% and can be improved with postoperative radiotherapy, with reports ranging from 27% to 40%, and up to 80%.[115,122,124,140] Median overall survival is frequently reported to be between 2 and 3 years, though median overall survival of longer than 5 years has been reported in some series. Data from the population-based SEER Registry showed a 5-year overall survival of approximately 60% for all patients classified as having malignant meningiomas, though lack of central review makes it possible that some of these patients truly had lower-grade tumors. In most studies, greater extent of resection (Simpson grade) and use of adjuvant radiation therapy are favorable prognostic factors.

When tumors recur after the exhaustion of all reasonable treatment options, adequate supportive treatment and palliative care are the major objectives. Headache due to infiltration/compression of the meninges and/or cranial nerves or other pain-sensitive structures; seizures; raised intracranial pressure; hydrocephalus; and brain edema are the most frequent clinical signs and symptoms. Physicians experienced in the palliative care of brain tumor patients should be involved at this time, if not before.

Conclusion

Despite the high incidence of meningioma, advances in the clinical care of patients with meningiomas have been occurring more slowly than advances in other relatively common nervous system tumors such as high-grade glioma and brain metastases. While neurosurgical and radiation therapy techniques continue to improve over time, fundamental questions remain about how to best use these treatments. Ongoing trials will provide insight into some open questions such as the optimal timing of radiation therapy after gross total resection of WHO grade II meningioma and the efficacy of targeted chemotherapy agents. Recent consensus statements regarding endpoint selection should make future radiation and chemotherapy trials more readily comparable to one another. For now, areas of uncertainty and debate among clinicians should be clearly explained to patients so that fully informed decisions can be reached.

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